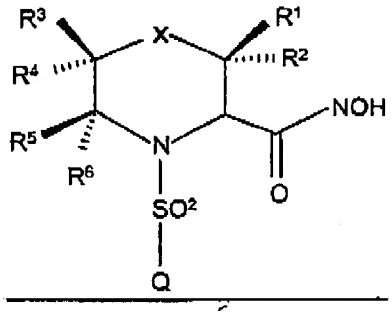
IN THE CLAIMS:

Claims 1 - 60 (Cancelled)

Claim 61 (Currently Amended) A method of inhibiting the cleavage of TNF-α from cell membranes in a human comprising administering to such human an effective amount of a hydroxamic acid compound comprising ~~a suitable substituted~~ the formula:



or the pharmaceutically acceptable salt thereof, wherein

X is oxygen, sulfur, SO, SO_2 or NR^7;

R^1, R^2, R^3, R^4, R^5 and R^6 are selected from the group consisting of hydrogen, hydroxy, NH_2, -CN, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_6-C_{10})aryl(C_2-C_6)alkenyl, (C_2-C_9)heteroaryl(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_6-C_{10})aryl(C_2-C_6)alkynyl, (C_2-C_9)heteroaryl(C_2-C_6)alkynyl, (C_1-C_6)alkylamino, $[(C_1-C_6)alkyl]_2$amino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, perfluoro(C_1-C_6)alkyl, perfluoro(C_1-C_6)alkoxy, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_2-C_9)heteroarylamino, (C_2-C_9)heteroarylthio, (C_2-C_9)heteroaryloxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkyl(hydroxymethylene), piperidyl, (C_1-C_6)alkylpiperidyl, (C_1-C_6)acyl,(C_1-C_6)acylamino, (C_1-C_6)acylthio, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy-(C=O)-, $-CO_2H$, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, and $[(C_1-C_6)alkyl]_2$-N-(C=O)-;

wherein said (C_1-C_6)alkyl is optionally substituted by one or two groups selected from (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, trifluoromethyl, halo, -CN, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_2-C_9)heteroarylamino, (C_2-C_9)heteroarylthio, (C_2-C_9)heteroaryloxy, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, hydroxy, piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy, (C_1-C_6)acylamino, (C_1-C_6)acylthio, (C_1-C_6)acyloxy, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, amino, (C_1-C_6)alkylamino or ((C_1-C_6)alkyl)$_2$amino;

R^7 is hydrogen; (C_1-C_6)alkyl optionally substituted by one or more of hydroxy, -CN, (C_1-C_6)alkylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, perfluoro(C_1-C_6)alkyl, (C_6C_{10})aryl, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_2-C_9)heteroarylamino, (C_3-C_6)cycloalkyl, (C_1-C_6)alkyl(hydroxymethylene), piperidyl, (C_1-C_6)alkylpiperidyl, (C_1-C_6)acyl, (C_1-C_6)acylamino, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy-(C=O)-, -CO_2H, (C_1-C_6)alkyl-NH-(C=O)-, and [(C_1-C_6)alkyl]$_2$-N-(C=O)-; (C_6-C_{10})arylsulfonyl; (C_1-C_6)alkylsulfonyl; (C_1-C_6)alkyl-NH-(C=O)-; (C_1-C_6)alkoxy-(C=O)-; (C_1-C_6)alkyl-(C=O)-; [(C_1-C_6)alkyl]$_2$-N-(C=O)-; or (R^8R^9N)-(C=O) where R^8 and R^9 are taken together with the nitrogen that they are attached to form a ring selected from azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl and thiomorphonyl; where Q is (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl,(C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_{10})heteroaryl, (C_1-C_{10})heteroaryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl(C_1-C_6)alkoxy(C_1-C_{10})heteroaryl;

with the proviso that when X is SO or SO_2 and R_3 and R_4 are a substituent comprising a heteroatom, the heteroatom cannot be bonded to the ring;

and with the proviso that at least one of R^1-R^6 must be (C_1-C_6)alkyl;

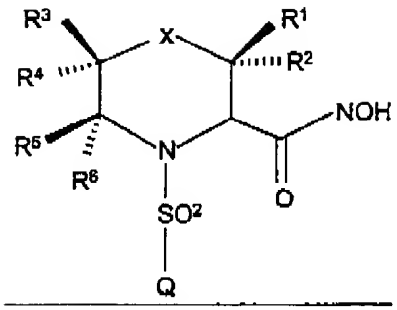
and with the proviso that when X is oxygen or sulfur and R^3-R^6 are each hydrogen then R^1 and R^2 cannot both be methyl;

that possesses an in vitro IC_{50} selectivity for TACE over MMP-1 of at least 100 fold; wherein MMP-1 activity is determined by an MMP-1 in vitro assay and wherein TACE activity is determined by a human monocyte assay.

Claims 62 – 80 (Cancelled)

Claim 81 (Currently Amended) ~~A method of inhibiting the cleavage of TNF-α from cell membranes in a human comprising administering to such human an effective amount of a disubstituted hydroxamic acid compound comprising a suitably substituted (C6-C10)aryl(C1-C6)alkoxy(C6-C10)aryl, (C6-C10)aryl(C1-C6)alkoxy(C1-C10)heteroaryl, (C1-C10)heteroaryl(C1-C6)alkoxy(C6-C10)aryl, or (C1-C10)heteroaryl(C1-C6)alkoxy(C1-C10)heteroaryl, that~~ The method of claim 61 wherein said hydroxamic acid compound possesses an in vitro IC_{50} selectivity for TACE over MMP-1 of at least 500 fold; wherein MMP-1 activity is determined by an MMP-1 in vitro assay and wherein TACE activity is determined by a human monocyte assay.

Claim 82 (Currently Amended) A method of inhibiting the cleavage of TNF-α from cell membranes without inhibiting MMP-1 in a mammal comprising: administering to said mammal an effective amount of a hydroxamic acid compound that possesses at least 100 fold IC_{50} selectivity for TACE over MMP-1, said hydroxamic acid compound comprising ~~a~~ the formula:



or the pharmaceutically acceptable salt thereof, wherein

X is oxygen, sulfur, SO, SO_2 or NR^7;

R^1, R^2, R^3, R^4, R^5 and R^6 are selected from the group consisting of hydrogen, hydroxy, NH_2, -CN, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_6-C_{10})aryl(C_2-C_6)alkenyl, (C_2-C_9)heteroaryl(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_6-C_{10})aryl(C_2-C_6)alkynyl, (C_2-C_9)heteroaryl(C_2-C_6)alkynyl, (C_1-C_6)alkylamino, $[(C_1-C_6)alkyl]_2$amino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, perfluoro(C_1-C_6)alkyl, perfluoro(C_1-C_6)alkoxy, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_2-C_9)heteroarylamino, (C_2-C_9)heteroarylthio, (C_2-C_9)heteroaryloxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkyl(hydroxymethylene), piperidyl, (C_1-C_6)alkylpiperidyl, (C_1-C_6)acyl, (C_1-C_6)acylamino, (C_1-C_6)acylthio, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy-(C=O)-, $-CO_2H$, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, and $[(C_1-C_6)alkyl]_2$-N-(C=O)-;

wherein said (C_1-C_6)alkyl is optionally substituted by one or two groups selected from (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, trifluoromethyl, halo, -CN, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_2-C_9)heteroarylamino, (C_2-C_9)heteroarylthio, (C_2-C_9)heteroaryloxy, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, hydroxy, piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy, (C_1-C_6)acylamino, (C_1-C_6)acylthio, (C_1-C_6)acyloxy, $(C_1-$

C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, amino, (C_1-C_6)alkylamino or ((C_1-C_6)alkyl)$_2$amino;

R^7 is hydrogen; (C_1-C_6)alkyl optionally substituted by one or more of hydroxy, -CN, (C_1-C_6)alkylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, perfluoro(C_1-C_6)alkyl, (C_6C_{10})aryl, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_2-C_9)heteroarylamino, (C_3-C_6)cycloalkyl, (C_1-C_6)alkyl(hydroxymethylene), piperidyl, (C_1-C_6)alkylpiperidyl, (C_1-C_6)acyl, (C_1-C_6)acylamino, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy-(C=O)-, -CO_2H, (C_1-C_6)alkyl-NH-(C=O)-, and [(C_1-C_6)alkyl]$_2$-N-(C=O)-; (C_6-C_{10})arylsulfonyl; (C_1-C_6)alkylsulfonyl; (C_1-C_6)alkyl-NH-(C=O)-; (C_1-C_6)alkoxy-(C=O)-; (C_1-C_6)alkyl-(C=O)-; [(C_1-C_6)alkyl]$_2$-N-(C=O)-; or (R^8R^9N)-(C=O) where R^8 and R^9 are taken together with the nitrogen that they are attached to form a ring selected from azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl and thiomorphonyl; where Q is (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl,(C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl,(C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, or (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl wherein each of said (C_6-C_{10})aryl or (C_2-C_9)heteroaryl groups may optionally be substituted by one of more substituents independently selected from halo, -CN, (C_1-C_6)alkyl optionally substituted with one or more fluorine atoms, hydroxy, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy optionally substituted with one or more fluorine atoms, (C_1-C_6)alkoxy(C_1-C_6)alkyl, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, HO-(C=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-O-(C=O)- (C_1-C_6)alkyl, (C_1-C_6)alkyl-(C=O)-O-,(C_1-C_6)alkyl(C=O)-O-(C_1-C_6)alkyl, H(O=C), H(O=C)-(C_1-C_6)alkyl, (C_1-C_6)alkyl(O=C)-, (C_1-C_6)alkyl(O=C)- (C_1-C_6)alkyl, NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, [(C_1-C_6)alkyl]$_2$amino(C_1-C_6)alkyl, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-

C_6)alkyl]$_2$N-(C=O)-, $H_2N(C=O)$- (C_1-C_6)alkyl, (C_1-C_6)alkyl-HN(C=O)- (C_1-C_6)alkyl, [(C_1-C_6)alkyl]$_2$N-(C=O)-(C_1-C_6)alkyl, H(O=C)-NH-, (C_1-C_6)alkyl(C=O)-NH, (C_1-C_6)alkyl(C=O)-[NH] (C_1-C_6)alkyl, (C_1-C_6)alkyl(C=O)-[N(C_1-C_6)alkyl] (C_1-C_6)alkyl, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-(S=O)-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-SO_2-[N-(C_1-C_6)alkyl]-, H_2N-SO_2-, H_2N-SO_2-(C_1-C_6)alkyl, (C_1-C_6)alkylHN-SO_2-(C_1-C_6)alkyl, [(C_1-C_6)alkyl]$_2$N-SO_2-(C_1-C_6)alkyl, CF_3SO_3-, (C_1-C_6)alkyl-SO_3-, phenyl, phenyl(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_9)heterocycloalkyl, and (C_2-C_9)heteroaryl;

with the proviso that when X is SO or SO_2 and R_3 and R_4 are a substituent comprising a heteroatom, the heteroatom cannot be bonded to the ring;

and with the proviso that at least one of R^1-R^6 must be (C_1-C_6)alkyl;

and with the proviso that when X is oxygen or sulfur and R^3-R^6 are each hydrogen then R^1 and R^2 cannot both be methyl; wherein MMP-1 activity is determined by an MMP-1 in vitro assay and wherein TACE activity is determined by a human monocyte assay.

Claim 83 (Original) The method of Claim 82 wherein said hydroxamic acid compound possesses at least 500 fold IC_{50} selectivity for TACE over MMP-1.